The Management of Agitated Toxidromes

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KEYWORDS

• Agitation • Sedation • Hyperthermia • Cooling • Intoxication

KEY POINTS

- Agitated patients are medical emergencies with potential life-threatening conditions and must be evaluated in a critical care area to rapidly control their behavior.
- Physical restraints are temporizing measures to provide patient and staff safety while pharmacologic sedation is achieved to promptly allow a thorough physical examination.
- Complete vital signs including capillary glucose and core temperature are needed within minutes of arrival to detect and treat hyperthermia or hypoglycemia and other life-threatening conditions.
- Fast-acting benzodiazepines are preferred for unknown agitated patients while parenteral droperidol is a safe and effective option whereby available.
- Specific antidotal therapy is rarely indicated in the initial management of agitated patients.

INTRODUCTION

The assessment and treatment of patients with psychomotor agitation is a common clinical situation in emergency medicine. These patients are often challenging in that some are gravely ill, and many pose a significant threat not only to their own safety but also to the safety of other patients in the emergency department as well as the hospital staff. Health care teams need to develop a rapid, organized, and safe approach to the behavioral control, diagnosis, and management of agitated patients.

Historically, the care of agitated patients was relegated to psychiatry services and included practices such as seclusion, prolonged use of full-body restraints with straitjackets or other devices, and in the 1970s large doses of potent and long-acting antipsychotics.[1] These practices often neglected underlying medical conditions or

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allowed patients to suffer complications and even death from hyperthermia, fluid and electrolyte abnormalities, and oversedation with subsequent aspiration pneumonitis. Even in the modern era, inappropriate pharmacotherapy for agitation that produced lethal serotonin toxicity reshaped graduate medical education in the United States[2,3] and shifted the focus of care of agitated patients to emergency physicians.

It is noteworthy that in many of the foundational studies that address the appropriate pharmacologic options for agitated patients, a large percentage are ultimately diagnosed with toxicologic conditions, most commonly alcohol intoxication or sympathomimetic toxicity.[4–11] However, because the initial diagnosis of many patients is unclear or completely unknown, their abnormal behavior should be approached as an emergency and dealt with in an appropriate acute care area such as the resuscitation bay. In this way life-threatening conditions such as hypoglycemia, hyperthermia, or epidural hematoma can be rapidly identified and treated. While this article focuses on the diagnosis and treatment of agitated toxicology patients, it also discusses safe and effective strategies for patients with undifferentiated agitation. For the purposes of this article, we use the following definitions:

- Agitation: A psychomotor abnormality that results in physical behavior that is either harmful to the patient or staff or prevents a rapid thorough medical assessment.
- Undifferentiated agitation: Patients for whom the etiology of their agitation is not conclusive based on history and a rapid physical assessment and for whom laboratory investigations and other tests are usually warranted.

The differential diagnosis for agitation is extensive and includes infectious, metabolic, toxicologic, psychiatric, traumatic, electrolyte, and endocrine abnormalities among others. An extensive discussion of the mechanisms for each of these possibilities is beyond the scope of this article. Rather we will focus on the common toxicologic causes (**Table 1**).

ASSESSMENT

Traditionally, the medical evaluation begins with obtaining a complete history followed by physical examination. However, agitated patients are often unable to provide much (if any) history, and behavioral control followed by a rapid physical assessment must take precedence for the safety of both the patient and hospital personnel. When multiple members of the health care team are available, one member should be assigned to obtain any possible collateral information about the patient from family, friends, emergency services personnel, or police, who accompany the patient to the hospital. Additional sources such as the electronic medical record should be queried for evidence of substance use disorders, psychiatric illness, pharmacotherapy, or medical comorbidities.

Patients should be brought immediately to a critical care area, such as a resuscitation bay. Doing so offers many advantages:

Table 1
Common toxicologic causes of agitation

Amphetamines	Ethanol intoxication
Anticholinergics	Ethanol and sedative hypnotic withdrawal
Cocaine	Ketamine and phencyclidine
Dissociative (ketamine and phencyclidine)	Serotonin toxicity

- It heightens the team's awareness that a life-threatening emergency may be occurring
- It provides access to monitoring and resuscitation equipment and in certain settings, imaging studies.
- It facilitates the rapid initial use and prompt the titration of intravenous sedation medications to achieve the desired behavioral effect.
- It allows sufficient space for multiple members to care for the patient in a safe environment.
- It removes the patient from the main emergency department to limit stress on other patients, family members, and providers.

The assessment of all patients begins with a full set of vital signs that includes blood pressure, heart rate, respiratory rate, core temperature, oxygen saturation, and a bedside determination of the blood glucose concentration. Agitated toxicology patients are most commonly hypertensive, tachycardic, tachypneic, and hyperthermic. The extent of these vital sign abnormalities is multifactorial and relate to the toxin, the individual and their preexisting conditions, the duration of the event, and ambient environmental conditions. Although no patient should ever be considered too agitated to obtain all vital signs, pharmacologic intervention is often required to measure a core temperature. Also, while abnormalities of blood pressure and heart rate can be dramatic, clinicians should be aware that unrecognized and or untreated hyperthermia likely poses the most immediate life threat. Although data are not available for all etiologies in the differential diagnosis noted above, the most illustrative data address the cause of lethality in cocaine toxicity. In a conscious animal model, rapid control of temperature was the single most important factor contributing to survival.[12] Additional support comes from epidemiologic evidence that demonstrates an increase in the fatality rate from cocaine as ambient temperatures climb.[13,14] Presumably this represents an inability to dissipate the heat generated during agitation as ambient temperature (and likely humidity) increase. As such, rather than defining behavioral control as the main outcome, we set the goals for a successful initial assessment as follows and divide our standard into 2 time frames:

- The first 10 minutes from presentation
  - Achieve physical control
  - Determine of vital signs including a bedside glucose measurement
  - Assure the adequacy of the airway, breathing, and circulation
  - Exclude trauma
  - Insert an intravenous catheter and if the IV is not successful after 1 to 2 attempts, expose an area for intramuscular administration
  - Begin pharmacologic sedation to achieve behavioral control
  - Treat hypoglycemia if present
  - Attach the patient to a cardiac monitor and continuous pulse oximetry and observe the rhythm strip
- The first 20 minutes
  - Obtain necessary blood specimens; electrolytes can be requested on a blood gas analyzer to rapidly exclude MDMA induced hyponatremia *before* fluid boluses
  - Begin treatment of hyperthermia if present
  - Obtain a 12-lead electrocardiogram if indicated
  - Begin volume resuscitation if indicated
  - Restore the patient to a clinical state in which physical restraint is no longer needed

It is essential to recognize that physical restraints are only indicated as a temporizing measure until behavioral control can be achieved by pharmacologic intervention. Prolonged physical restraint without adequate chemical sedation is inhumane and can lead to mechanical complications as well as severe psychological distress.

A complete physical assessment is necessary to help identify clues to traumatic injuries and medical disorders. The toxicologic physical examination focuses on skin, eyes, bowel, bladder, and muscle tone. **Table 2** highlights how an assessment of these organ systems can help differentiate among patients who, on initial evaluation may seem similar.

Individualized laboratory testing is recommended and often includes a complete blood count, electrolytes, hepatic and kidney function testing, creatine phosphokinase, and troponin. Targeted toxicology testing of co-ingestants (such as acetaminophen, ethanol, and known psychoactive medications) is also recommended in cases of suspected self-harm. In contrast, however, we discourage the routine use of urine testing for common drugs of abuse because turn-around times for testing are, in some settings, too long to influence acute management,[15] there are significant false positive and false negative results[16] that are too often misinterpreted by clinicians, and when studied these tests rarely if ever impact on acute patient care.[17–20] Many of our psychiatric colleagues use the results of urine drug testing to engage a conversation with patients with the dual diagnoses of substance use disorders and psychiatric illness. Because the results of urine drug testing rarely change over a short period of time, urine testing can be deferred until a time that the psychiatric team can evaluate its benefit in their intervention and recommend a more precise assay if available.

Similarly, the indications for neuroimaging should be individualized rather than included as part of the mandatory initial assessment. Sending patients prematurely for neuroimaging despite the lack of focal findings or signs of significant trauma while life-threatening hyperthermia, hypoglycemia, or hyponatremia are left untreated is dangerous. Neuroimaging should be deferred until the patient's ABCs are stabilized, and other immediately life-threatening abnormalities are addressed. When infectious central nervous system processes are highly suspected, administration of empirical antimicrobials is indicated, and lumbar puncture should only be performed when the patient can be positioned safely considering that modern PCR techniques improve the accuracy of delayed diagnosis.

Table 2
Common differentiating findings on physical examination

Organ System	Characteristic Findings
Skin	*Diaphoretic* with sympathomimetics, serotonin toxicity and ethanol and sedative hypnotic withdrawal *Dry* with anticholinergic toxicity
Eyes	*Mydriatic and briskly responsive to light* with sympathomimetics *Mydriatic and poorly responsive to light* with anticholinergics *Vertical and rotatory nystagmus* with phencyclidine and ketamine
Bowel sounds	*Active* with sympathomimetics, serotonin toxicity, and ethanol and sedative hypnotic withdrawal *Quiet or absent* with anticholinergic toxicity
Bladder	*Urinary retention* with anticholinergics, ketamine and phencyclidine
Muscle tone	*Spontaneous and inducible clonus* that is more pronounced in the legs than in the arms with serotonin toxicity

THERAPEUTIC INTERVENTIONS

Sedation

Perhaps there is no greater controversial topic in the treatment of the agitated patient than the choice of pharmacologic agents for behavioral control. Therapeutic options generally fall into one of the 3 categories: benzodiazepines (diazepam, lorazepam, midazolam), antipsychotics (haloperidol, droperidol, olanzapine) and dissociatives (ketamine). When the nature of the agitation is reasonably clear the literature supports optimal pairing of intervention with the disorder (**Table 3**).

However, when patients truly have undifferentiated agitation or possibly multiple concomitant causes of agitation the therapeutic option should be selected based on the preferred route of administration, the onset and duration of the effect, and the risk of adverse reactions. The following statements present evidence-based corrections to common misstatements conveyed in multiple scientific discussions:

- *Droperidol and risk of QT prolongation. Evidence: The use of droperidol in acutely agitated patients is not commonly associated with clinically significant QT interval prolongation.*[11]
- *Antipsychotic drugs lower seizure threshold. Evidence: Antipsychotics do not appear to lower seizure threshold or impair heat dissipation to a clinically degree in patients with sympathomimetic toxicity.*[21]
- *Olanzapine increases the risk of benzodiazepine-induced respiratory depression. Evidence:* Although the US FDA recently changed the labeling of olanzapine because of adverse drug events reported during postmarketing surveillance,[22] this is not supported by systematic review or prospective evaluations.[23–26]

Whenever possible, the use of intravenous administration is preferred over intramuscular administration. The faster onset of action and guaranteed systemic absorption allow more precise titration compared with the longer and erratic intramuscular absorption. The additional benefits of secured intravenous access allow for prompt laboratory testing and glucose or fluid administration. Knowledge of the pharmacokinetics and pharmacodynamic properties of each medication will guide the appropriate dose and interval of administration. Some general guidelines are provided in the following discussion.

Benzodiazepines

Three parenteral benzodiazepines are generally used; diazepam, lorazepam, and midazolam. For all indications, diazepam should never be used intramuscularly as the absorption is incomplete and unpredictable.[27–29] The pharmacodynamics of these drugs differ by indication in terms of relative times to peak and durations of effect. When used parenterally as an anticonvulsant all 3 drugs have a fairly rapid onset of action with midazolam showing some clinical superiority with regard to terminating seizures

Table 3
Potential Initial intervention for patients with known toxicologic diagnoses[a]

Diagnosis	Initial Intervention
Alcohol withdrawal	Benzodiazepine
Alcohol intoxication	Antipsychotic
Anticholinergic	Physostigmine
Cocaine	Benzodiazepine

[a] For diagnoses not listed in this table, data are insufficient to recommend one specific pharmacologic intervention over the others.

in adults,[30] whereas in children both lorazepam and midazolam have similar efficacy.[31] For seizure control, lorazepam also has the longest duration of action. However, with regard to sedation, these drugs behave quite differently. Midazolam and lorazepam are both predictably absorbed by the intramuscular route. The onset and peak effect of midazolam is fast, whereas the onset of action of lorazepam is slower, and the peak effect of lorazepam is delayed up to about 20 minutes regardless of the route of administration.[32–35] The sedation from lorazepam lasts longer than midazolam. Following a single dose, sedation from lorazepam may last for as long as 4 hours[36] compared with 1 hour for midazolam.[37] Repeated dosing or continuous infusion delays the time to the restoration of consciousness. Following the termination of a 1 to 2-day continuous infusion, sedation lasted 8.7 hours from lorazepam versus 3.0 hours from midazolam.[38] Because of the delayed to peak effect of lorazepam there is a tendency to over-sedate patients when repeated dosing is necessary. This occurs because the peak effect has not occurred from the first dose at a time when subsequent doses are being given. Midazolam is preferable when rapid behavioral control or possible titration is necessary. Although the short duration of effect requires frequent repeat administration, this also allows clinical reevaluation and helps prevent oversedation. As the cause of agitation is properly diagnosed over time, other medications can be administered with longer duration of effects.

Antipsychotics

In multiple controlled trials parenteral olanzapine, haloperidol, droperidol, and ziprasidone safely and effectively produce rapid control of agitated patients in an emergency department setting.[4,9–11] While the differences among these medications often reach statistical significance the clinical relevance of these differences are uncertain. Some distinctions are worth mentioning. The effects of midazolam are generally appreciated sooner than antipsychotics but are shorter in duration. As single therapies, droperidol and olanzapine have pharmacodynamic profiles that are more desirable than haloperidol or ziprasidone.

Controlled data do not support the preferential use of haloperidol at the typical doses studied. Most initial studies were performed in psychiatric patients in an era when adverse effects of oversedation were overlooked. Many clinicians still use relatively large doses of haloperidol. It should be noted, however, that based on studies that analyze dopamine receptor occupancy, parenteral doses of haloperidol of 5 mg are generally sufficient to maximize sedation in the average adult,[39] with greater doses only increasing the likelihood of extrapyramidal symptoms. Smaller adults likely warrant lower doses.

Ketamine

Success with the prehospital use of ketamine for trauma patients stimulated interest in ketamine use for agitation. While it is clear that ketamine produces rapid behavioral control, patients treated with ketamine are more likely to be admitted to the hospital and more likely to require endotracheal intubation than patients treated with other medications when a fixed standard dose of ketamine is administered irrespective of weight.[7,8,40] Because admission to an intensive care unit is a precious resource, the use of intramuscular ketamine as initial therapy should be reserved for situations in which insufficient personnel exist to safely physically restrain patients for intravenous access and/or situations for which the use of other medications are undesirable (eg, end-stage COPD or high BMI for benzodiazepines, hyperthermic patients and antipsychotic or borderline hypotension for both drug classes). When other medications have failed, there is sufficient literature support for the use of ketamine as a second-line or "rescue" medication.[41]

Combination Therapies

The choice to begin with combination therapies (usually an antipsychotic plus a benzodiazepine) is again rooted in the treatment of patients on psychiatric wards making a distinction between rapid tranquilization (ie, behavioral control) and rapid neuroleptization (ie, psychiatric control).[42] This practice is based on a theory of a broad spectrum pharmacologic approach that limits the doses of each medication to maximize individual adverse-effect profiles and gave rise to the common practice of "5 and 2" (5 mg of haloperidol combined with 2 mg of lorazepam). It does, however, increase the risks of an adverse interaction between the 2 therapies. We want to reiterate that the use of midazolam is superior to lorazepam in patients who require rapid behavioral control and that the practice of combined lorazepam and antipsychotic therapy predates the wider availability of midazolam. One study comparing the intramuscular use of 10 mg of midazolam to either 10 mg of droperidol intramuscularly or the combined use of 5 mg of each drug supported this practice noting a similar time to achieve behavioral control in all groups and more adverse airway effects (desaturation or airway obstruction) in the midazolam only group.[11] Additionally, the routine use of diphenhydramine or another anticholinergic is discouraged because of concerns of QRS and QT interval prolongation and the false pharmacologic claim that it prevents dystonic reactions (which are usually delayed by at least 24 hours) when coadministered with antipsychotics.

Existing Guidelines

Guidance exists from white papers,[43] best practice statements in emergency medicine,[44] and consensus statements from psychiatry,[45] and psychopharmacology.[46] These statements do not provide convincing evidence to support any particular pharmacologic approach in patients with undifferentiated agitation and are therefore only included for completeness.

Cooling

Untreated hyperthermia can lead to cerebral edema, myocardial dysfunction, and disseminated intravascular coagulopathy (DIC). It is common for patients who are insufficiently cooled to survive the acute event only to develop these complications 12 to 48 hours after presentation.[47] As the core temperature increases a cascade of events leads to increased intestinal permeability to endotoxin[48] resulting in a clinical syndrome that resembles gram-negative sepsis.

There is a critical time and temperature beyond which irreversible damage is likely to occur. In animal models of heatstroke this varies by species studied and ranges from 12 minutes at 43.5 °C in rabbits[49] to 23 minutes at 42 °C in rats[50] and 68 minutes at 44 °C in dogs.[51] For obvious reasons, data on human toxicology patients are lacking, but heatstroke references often use critical core temperatures of 40 °C[52] to 40.5 °C[52,53] When considering the animal data and recognizing that patients usually become hyperthermic in the prehospital setting; activation of emergency services and transport to the hospital take some time; and that patients must then be assessed before hyperthermia is confirmed, cooling must begin rapidly and proceed as efficiently as possible. Thus from the time of recognition, the goal should be to cool the patient to a near-normal core temperature in 20 minutes or less. This requires an organized and practiced approach to cooling.

Debate continues over optimal cooling methods, with physicists supporting evaporative cooling and others championing immersion in cold water. In a human volunteer model of exertional heatstroke a specialized evaporative cooling device produced

cooling rates as rapid as 0.30 °C/min which was better than the 0.19 °C/min rate in a tepid water bath.[54] However, when used in real-world conditions, many of the sickest patients required more than 1 hour to cool to a normal temperature.[55] In contrast, immersion of hyperthermic volunteers in water at 2 °C produced a mean cooling rate of 0.35 °C/min) and was not associated with shivering.[56] By comparison, cooling rates in 2 agitated hyperthermic toxicology patients who were placed in ice baths were 0.18 °C/min and 0.28 °C/min[57] These rates are not achievable with ice blankets, customized external cooling devices, or endovascular devices designed for postresuscitation care. In fact, one recent systematic review of the treatment of exertional heatstroke concluded that cooling rates faster than 0.15 °C/min were positively associated with increased survival and that cold water immersion was essential to reduce complications and maximize survival.[53] Another systematic review of both exertional and nonexertional heatstroke concluded that ice water immersion was the most efficient cooling technique.[52]

In practice, agitated patients with core temperatures in excess of 40.5 °C require sedation (see section above on the choice of sedatives) and occasionally paralysis postintubation based on their clinical condition and immersion in an ice and water bath as previously described.[57] Continuous monitoring of vital signs are maintained and core temperature is measured via a flexible rectal probe or one included as part of a urinary catheter. Patients are maintained in the bath until their core temperature approaches 38 °C at which point they are removed, dried, and placed on a stretcher. This generally prevents hypothermia as patients continue to cool during the moving and drying process. Recurrent hyperthermia is uncommon as long as sedation is maintained until the physiologic effects of the toxin resolve.

For settings in which ice and water bath immersion or cooling devices are not available, another option is to cover both the back, thorax, abdomen, and limbs of the patient in towels submerged in ice water and change the towels frequently. The addition of a fan is desirable.

Antidotes for Toxin-Specific Receptor Antagonism

Physostigmine

Although the cholinesterase inhibitor physostigmine was once used reflexively in the empiric treatment of poisoned patients with altered mental status,[58] this practice fell out of favor when several authors reported serious and sometimes lethal adverse effects when physostigmine was given to patients with tricyclic antidepressant poisoning.[59–61] Subsequent confusion over the risks, benefits, indications, and contraindications resulted in a near abandonment of physostigmine use. Fortunately, several retrospective studies suggested that the judicious use of physostigmine in patients with suspected anticholinergic poisoning could safely reverse agitation, delirium and reduce unnecessary testing.[62–65] Recently, a small randomized controlled trial demonstrated that when compared with lorazepam, patients given physostigmine had better control of their agitation and anticholinergic delirium.[66]

The life-threatening manifestations of isolated antimuscarinic toxicity (ie, anticholinergic toxicity in the absence of cardiovascular complications from anticholinergic drugs such as tricyclic antidepressants) generally relate to psychomotor agitation and its complications namely hyperthermia and rhabdomyolysis. As such, the generic approach to sedation and proactive care of agitated toxicology patients discussed above is more than sufficient to protect patients from the complications of antimuscarinic toxicity. However, when that approach is selected many of these patients will become deeply sedated, require critical care admissions, and be subjected to unnecessary testing such as CT scans and lumbar punctures as they will often be

hyperthermic and altered. Physostigmine should be used in selected patients who are clinically antimuscarinic, have a normal QRS duration on their ECG, and would otherwise need physical restraint followed by chemical sedation. For these patients, physostigmine will not only confirm the diagnosis but also awaken the patient to allow thorough history taking, a psychiatric interview if necessary, and reduce unnecessary testing. Consultation with a regional poison center or a local medical toxicologist can help with this assessment.

Cyproheptadine

Serotonin toxicity results from single or combined use of drugs that stimulate mostly the 5-HT_{2A} and also possibly the 5-HT_{1A} receptors. Drugs that increase presynaptic stores (MAO inhibitors), promote release (amphetamines) or block reuptake (SSRIs, cocaine, meperidine) of serotonin are commonly implicated. Experimental animal models[67] and human case reports[68,69] suggest a potential role for cyproheptadine as an adjunct in the care of these patients. However, given that the major life threats are agitation and hyperthermia, that cyproheptadine is not available in a parenteral formulation, and that in select acute overdoses gastrointestinal decontamination with activated charcoal might be warranted, cyproheptadine's role is limited but is reasonable for mild cases of serotonin toxicity.

Dantrolene

Dantrolene is the drug of choice for malignant hyperthermia, a rare genetic disorder of the ryanodine receptor that leads to hyperthermia after exposure to inhalation anesthetics, succinylcholine, and other even less common drugs and conditions. Simply because a condition results in temperature elevation and adverse outcomes it is not always "malignant hyperthermia" and treatment with dantrolene is not indicated by analogy.[70,71] Attempts to find and administer dantrolene to patients who do not have malignant hyperthermia can lead to delays in life-saving interventions, specifically sedation and cooling. Dantrolene is, therefore, not indicated as a first-line therapy in patients with a low likelihood of malignant hyperthermia based on historical considerations. It can, however, be administered after sedation and cooling are started if malignant hyperthermia is suspected and muscle relaxation is refractory to neuromuscular blockade.

SUMMARY

Patients with agitated toxidromes span severities of illness from conditions as benign as alcohol intoxication to sympathomimetic toxicity with life-threatening hyperthermia. Even when the etiology seems toxicologic in nature these patients not only have the ability to sustain trauma but also by their behavior injure health care providers, other patients, and their families, and disrupt an entire emergency department. Emergency departments need to develop organized protocols for the assessment and treatment of these patients that recognize the potential for a high-acuity condition, provide a safe environment for all involved, minimize the use and duration of physical restraints, and immediately identify and treat life-threatening conditions. When the etiology is clearly known, specific interventions can be directed at the underlying pathology such as the preferred use of benzodiazepines in patients with alcohol withdrawal. When the etiology is undifferentiated the choice of pharmacotherapy is largely driven by provider experience and institutional protocols. The available data suggest that the differences in the onset and duration of behavioral control could be tailored to the individual needs of the patient. Understanding the pharmacokinetics and pharmacodynamics of these drugs is essential to such an approach. The goal of behavioral control should not be

limited to the restoration of a calm state, but rather to the time to attain a full set of vital signs including a core temperature and a rapid glucose concentration, establish intravenous access and send desired laboratory investigations, perform a focused physical examination, and begin resuscitation and cooling if needed.

CLINICS CARE POINTS

- Hyperthermia from sympathomimetics is most quickly treated with immersion in bath water.
- Physostigmine is safe to use in a pure anticholinergic toxidrome.
- Intravenous use of sedatives achieves behavioral control faster than intramuscular administration and should be preferred in severely agitated patients.

DISCLOSURE

The authors have nothing to disclose.

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